FOREWORD

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ABSTRACT

The effect of both mild and severe acute alkalosis, due to intravenous sodium bicarbonate infusion, on glomerular filtration rate, renal plasma flow, and sodium and potassium clearance was investigated on 12 anesthetized dogs. The maximum load used was over 50 gm. of $NaHCO_3$ administered intravenously in 4 hours, at a rate of 2.5 mEq./minute. On a weight basis, in a 70 kg. man, this would be equivalent to a load of 195 gm. of $NaHCO_3$ given at the rate of nearly 10 mEq./minute. The plasma potassium fell from 3.8 to 2.7 mEq./liter, and the plasma sodium increased from 144.4 to 170.8 mEq./liter with maximum $NaHCO_3$ loading. There was no apparent acute detrimental renal effect. No depression of glomerular filtration rate nor of renal plasma flow was seen in any series although the pH increased from 7.32 to 7.61. Similarly no significant effect was seen on blood pressure, hematocrit, filtration fraction, heart rate, or rectal temperature in any series. Urine flow and urine pH increased significantly with higher loading rates and concentrations.

This technical documentary report has been reviewed and is approved.

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EFFECT OF MASSIVE SODIUM BICARBONATE INFUSION ON RENAL FUNCTION

1. INTRODUCTION

In a previous study it was shown that glomerular filtration rate and renal blood flow are not altered by an increase in arterial pH due to hyperventilation (1). It has been claimed, however, that prolonged administration of sodium bicarbonate causes reduction in various parameters of renal function (2-7). Whether acute alkalosis due to sodium bicarbonate loading would lead to a similar finding was not clear. Maegraith et al. (8) found some evidence of reduction of function in a group of three patients given alkali for one to three days, while Van Goidsenhoven et al. (9) did not find any reduction in function during a period of three weeks of oral loading in man. Other studies are similarly contradictory (10-14). The purpose of this study was to investigate the effect of both mild and severe acute alkalosis, due to intravenous sodium bicarbonate loading, on glomerular filtration, renal plasma flow, and sodium and potassium clearance.

2. METHODS

Twelve dogs were used in this study. The animals were anesthetized with 30 mg. kg. of sodium pentobarbital, and tracheal intubation was performed at the outset. Stainless steel cannulae were implanted in the right femoral artery and vein. The arterial cannula served as a source for blood samples, while the venous cannula was used to give the prime dose of compounds introduced to measure renal function, the sustaining solution, and additional anesthetic as required. The ureters were cannulated with polyethylene tubing (PE 160) through an abdominal incision close to the bladder, to allow timed, quantitative, anaerobic urine collections under paraffin oil. An additional femoral artery was routinely cannulated to allow measurement of mean arterial blood pressure with a mercury manometer.

Creatinine clearance was used as a measure of glomerular filtration rate (GFR), and para-aminohippuric acid (PAH) clearance, at low plasma concentration, was used as a measure of renal plasma flow (RPF). Creatinine was determined by the method of Bonsnes and Taussky (15), and PAH was determined by the method of Bratton and Marshall (16) as modified by Smith et al. (17). Forty-five minutes before the experiment began, a priming dose of 0.1 gm. PAH and 0.5 gm. creatinine in 25 cc. of saline was given followed by a continuous infusion of a solution containing PAH, creatinine, and the test solute (NaCl during the pre-control and control periods and NaCl or $NaHCO_3$ during the remainder of the experiment). The concentrations and infusion rates varied in the different groups and will be outlined in detail below. After 45 minutes of equilibration, two control periods of 15 minutes each were conducted. Arterial blood samples were taken at the midpoint of each period for clearance determinations. After the control periods, $NaHCO_3$ was added to the experimental infusate, and serial and continual 30-minute clearance periods were conducted for the remainder of the experiment. The level of alkalosis was ascertained by measurement of anaerobic pH at both the midpoint and end of each clearance period with a Beckman model G pH meter and Beckman model 290-31 anaerobic blood electrode assembly immersed in a constant temperature bath set at 38° C. The pH of anaerobically collected urine samples was measured with the same setup. The total solids in plasma were measured with an A.O. Spencer hand refractometer (T.S. meter). Plasma and urine total CO_2 were measured by standard

TABLE I

Effect of large $NaHCO_3$ loads on renal function

	0.9% NaCl		5.2% $NaHCO_3$							
	Time (min.)									
	15	30	60	90	120	150	180	210	240	270
Rectal temp. (°C.)	37.0 ±0.6	37.0 ±0.6	36.7 ±0.7	36.6 ±0.7	36.6 ±0.8	36.6 ±0.8	36.7 ±0.9	36.7 ±0.9	36.8 ±1.0	36.8 ±1.0
Heart rate/min.	168 ±12	173 ±10	184 ±18	187 ±21	185 ±17	183 ±17	183 ±17	177 ±7	176 ±6	177 ±3
Mean arterial blood pressure (mm. Hg)	128 ±5	128 ±5	131 ±6	131 ±8	127 ±7	126 ±8	126 ±9	128 ±7	125 ±10	123 ±10
Change in body weight from start of pre-control infusion	.99 ±.15	1.23* ±.16	1.66* ±.17	1.95* ±.20	1.97* ±.29	1.64* ±.59	1.18 ±.83	.61 ±1.05	−0.08 ±1.25	−0.84 ±1.33
Anaerobic arterial pH	7.32 ±.01	7.33 ±.02	7.44* ±.02	7.52* ±.02	7.54* ±.02	7.56* ±.03	7.57* ±.03	7.57* ±.04	7.60* ±.04	7.61* ±.04
Anaerobic urine pH	5.91 ±.19	6.00 ±.13	6.55 ±.38	7.98* ±.10	8.05* ±.05	8.01* ±<.01	7.99* ±<.01	7.99* ±<.01	7.98* ±.01	7.97* ±.02
HCT (% RBC)	39.2 ±4.0	39.0 ±4.4	38.1 ±3.9	37.1 ±4.4	36.7 ±4.1	37.0 ±3.8	37.3 ±3.6	38.6 ±3.3	39.6 ±3.4	40.7 ±3.3
Total solids (gm. % in plasma)	7.9 ±.2	7.7 ±.2	7.5 ±.2	7.2 ±.2	7.1* ±.2	7.1* ±.1	7.1* ±.2	7.2 ±.2	7.4 ±.3	7.6 ±.4
Urine flow (ml./min.)	.24 ±.06	.23 ±.02	.40 ±.11	1.36 ±.54	2.77 ±1.05	4.64* ±1.81	5.57* ±1.61	6.28* ±1.22	7.05* ±1.47	7.36* ±0.87
GFR (ml./min.)	68.3 ±16.9	65.0 ±7.5	79.0 ±3.8	88.6 ±8.0	84.6 ±11.0	92.9 ±11.7	94.8 ±8.8	94.8 ±7.4	92.1 ±11.7	84.3 ±5.1
Clearance ratio for water (%)†	.34 ±.01	.41 ±.06	.51 ±.16	1.52 ±.59	3.11* ±.86	4.72* ±1.36	5.70* ±1.26	6.53* ±0.88	7.50* ±.63	8.68* ±.52
RPF (ml./min.)	199 ±54	177 ±22	200 ±8	218 ±9	211 ±27	233 ±30	246 ±28	252 ±9	256 ±7	231 ±17
Filtration fraction (%)	35.7 ±3.2	37.1 ±2.9	39.6 ±1.5	40.8 ±1.5	40.1 ±1.1	39.9 ±0.1	38.8 ±0.9	37.7 ±3.3	35.7 ±3.7	36.6 ±1.5

TABLE I (Contd.)

	0.9% NaCl		5.2% $NaHCO_3$							
	Time (min.)									
	15	30	60	90	120	150	180	210	240	270
Renal blood flow (ml. min.)	340 ±113	298 ±57	326 ±27	351 ±39	343 ±60	377 ±64	342 ±49	413 ±29	428 ±33	395 ±50
Renal resistance‡	.45 ±.09	.46 ±.08	.40 ±.02	.38 ±.02	.39 ±.06	.39 ±.05	.38 ±.03	.30 ±.02	.29 ±.03	.31 ±.02
Urine Na conc. (mEq. liter)	37.5 ±21.0	37.3 ±24.9	87.1 ±32.9	240.5* ±15.7	263.4* ±6.6	263.6* ±10.7	258.4* ±42.3	255.6* ±5.9	252.6* ±6.6	253.4* ±10.9
Plasma Na conc. (mEq./liter)	144.4 ±2.7	144.9 ±2.2	147.7 ±1.8	153.2* ±0.6	157.1* ±2.9	158.2* ±4.2	160.4* ±3.4	162.0* ±3.2	166.7* ±2.3	170.8* ±2.4
Clearance of Na from plasma (ml. min.)	.08 ±.05	.07 ±.05	.28 ±.15	2.17* ±.81	4.55* ±1.61	7.40* ±2.47	8.70* ±2.02	9.78* ±1.52	10.60* ±1.95	10.93* ±1.34
Clearance ratio for Na (%)	.06 ±.06	.07 ±.07	.36 ±.22	2.43 ±.96	5.14* ±1.29	7.62* ±1.73	8.97* ±1.42	10.22* ±.94	11.32* ±.67	12.86* ±.94
Urine K conc. (mEq./liter)	101.9 ±8.1	120.5 ±9.1	145.6 ±16.6	101.8 ±26.2	51.9* ±11.2	35.5* ±7.4	28.4* ±7.2	21.8* ±2.8	19.9* ±3.0	15.8* ±1.3
Plasma K conc. (mEq./liter)	3.81 ±.23	3.85 ±.25	3.77 ±.20	3.40 ±.17	3.08* ±.08	2.96* ±.06	2.95* ±.11	2.77* ±.24	2.70* ±.28	2.71* ±.25
Clearance of K from plasma (ml./min.)	6.3 ±1.7	7.0 ±.6	15.1 ±3.9	32.9* ±4.4	38.9* ±4.3	46.5* ±6.4	45.8* ±1.1	47.1* ±.8	49.0* ±.4	42.5* ±1.2
Clearance ratio for K (%)	9.2 ±.3	10.8 ±.3	19.5 ±5.7	36.4* ±4.1	46.2* ±.9	50.0* ±1.5	49.8* ±5.3	50.3* ±3.7	54.9* ±7.3	50.7* ±1.9

Means and standard errors of the mean for 3 dogs in series 3B. Average weight of animals was 17.9 ± 1.1 kg. A prime dose of 0.5 gm. creatinine plus 0.1 gm. PAH in 25 ml. saline was given, followed by a 45-minute pre-control infusion of 0.75% creatinine and 0.1% PAH in 0.9% NaCl at 3.7 ml. minute. Two control clearance periods of 15 minutes each were then conducted while the infusion composition and rate were maintained as during the pre-control period. At the conclusion of the second control clearance, the infusion solution was changed to 0.75% creatinine and 0.1% PAH in 5.2% $NaHCO_3$. The average infusion rate was again 3.7 ml. minute. This infusion was maintained for 4 hours during which time eight 30-minute clearance periods were conducted.

*Statistically significant from control as a result of Fisher's t-test ($P<.05$).

†Clearance of substance / 100/GFR.

‡Mean arterial blood pressure / renal blood flow.

volumetric Van Slyke technic. Plasma and urine bicarbonate were calculated from the Henderson-Hasselbalch equation. Corrections were made as suggested by Severinghaus et al. (18, 19, 20).

Three series of experiments were conducted, testing the effect of low (series 1), medium (series 2), and high (series 3) bicarbonate loads on renal function. In series 1 the experimental animals were given a 45-minute pre-control and a 30-minute control infusion of 1.5% creatinine plus 0.2% PAH in 0.9% NaCl at 2.0 ml. minute. After control, the infusion rate and creatinine and PAH concentration were maintained, but a 1.3% $NaHCO_3$ solution was substituted for the 0.9% NaCl for 90 minutes of infusion. Thereafter 2.6% $NaHCO_3$ was substituted for the 1.3% $NaHCO_3$ for 150 additional minutes of infusion. Series 2 was similar to series 1 except that the infusion rate was approximately 4.0 ml./minute throughout, and the creatinine and PAH concentrations were reduced to 0.75% and 0.1%, respectively. In series 3, the pre-control and the control infusion were similar to that given in series 2, but after control 5.2% $NaHCO_3$ was substituted for the 0.9% NaCl. This infusate was given for 240 minutes. Each series had a control experiment, in which NaCl was given throughout at an infusion rate similar to the experimental series of concern. In the control experiment for series 3, both the rate of infusion and the osmotic concentration of

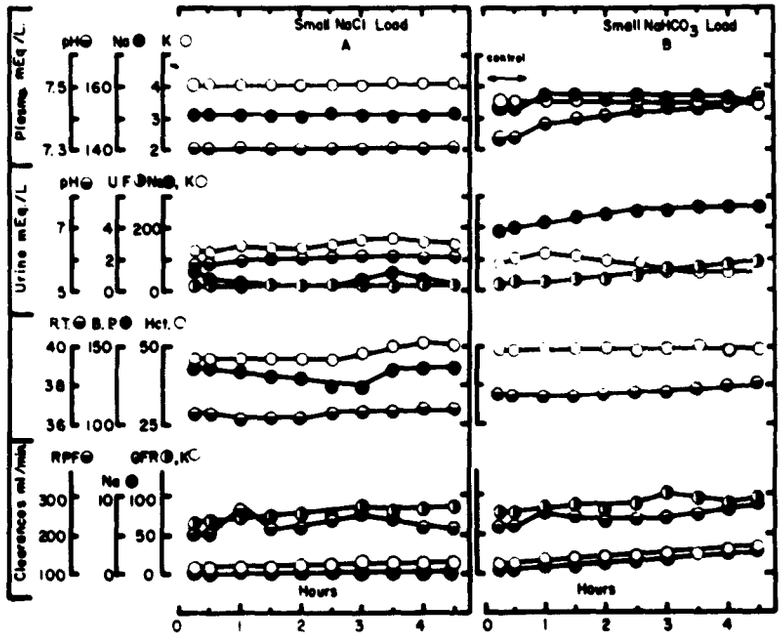

FIGURE 1

Plasma pH, Na and K concentration (mEq. liter); urine pH; urine flow (ml. minute); urine Na and K concentration (mEq. liter); rectal temperature (°C); blood pressure (mm. Hg); hematocrit; renal plasma flow, Na clearance, GFR, and K clearance (ml. minute) for 1 dog (1A) given 0.9% NaCl at 2.0 ml. minute for 45-minute pre-control, 30-minute control, and 240-minute test period. Average of 3 dogs (1B) handled as described above during pre-control periods, but given 1.3% $NaHCO_3$ at 2.0 ml. minute for 90 minutes, and then 2.6% $NaHCO_3$ at 2.0 ml. minute for 150 additional minutes during the test period. Dog weight in 1A was 22.1 kg.; average dog weight in 1B was 18.9 kg.

the NaCl solution were the same as for the $NaHCO_3$ solution used in the experimental dogs. Each of the three series had 3 experimental dogs and 1 control dog.

3. RESULTS

No depression of glomerular filtration or renal plasma flow was seen in any of the series although the arterial pH was elevated by bicarbonate loading from 7.33 to 7.47 in series 1 (fig. 1B), 7.31 to 7.57 in series 2 (fig. 2B), and 7.32 to 7.61 in series 3 (fig. 3B). Similarly no significant effect was seen on blood pressure, hematocrit, filtration fraction, heart rate, or rectal temperature in any series. A decrease in renal resistance did occur (table I). Owing to the large control variation and small sample, the fall in resistance was not statistically significant from control, but the renal resistances found during the last 90 minutes of infusion were significantly lower than the value obtained after 30 minutes of infusion. As expected, urine flow did increase significantly with higher loading rates and concentrations. Urine pH, in the series measured (series 2 and 3), reflected the excretion of bicarbonate. That the elevated urinary pH was not due to the diuresis per se was evident from the maintained acid urine pH in the control animals (figs. 1A-3A).

The metabolic alkalosis did significantly depress plasma K, 3.5 to 3.3 in series 1, 3.9 to 2.8 in series 2, and 3.8 to 2.7 in series 3 (figs. 1B-3B). No acute evidence of any det-

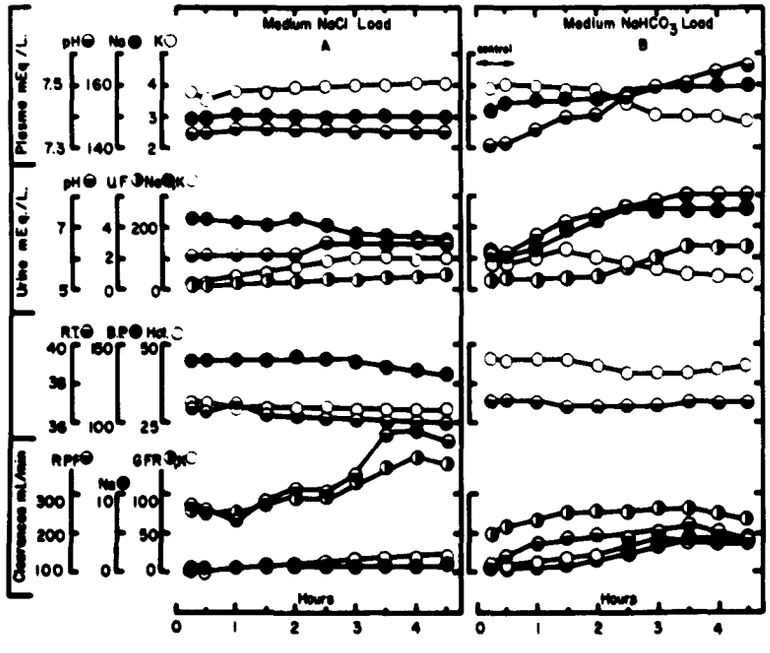

FIGURE 2

See legend for figure 1. Values are shown for 1 dog (2A) given 0.9% NaCl at 4.0 ml. minute for 45-minute pre-control, 30-minute control, and 240-minute test period. Average of 3 dogs (2B) handled as described above during pre-control and control periods, but given 1.3% $NaHCO_3$ at 4.0 ml. minute for 90 minutes, and then 2.6% $NaHCO_3$ at 4.0 ml. minute for 150 additional minutes during the test period. Dog weight in 2A was 22.2 kg.; average dog weight in 2B was 16.1 kg.

rimental renal effect of the latter levels of hypokalemia was seen. Though plasma K fell over 25% in series 2 and 3, the K excretion could only be accounted for by a depletion of intracellular stores, for the excreted K was greater than twice the original extracellular K content. The fall in plasma K was a resultant of the alkalosis as demonstrated by the failure of infusion of NaCl in the control runs (figs. 1A-3A) to cause any comparable decrease in plasma K. Because of hyperosmotic solute loading in series 2 and 3, there was in addition, some physical dilution of K concentration due to expansion of the extracellular space.

In series 3 (table I; fig. 3B), elevation of plasma sodium to levels over 170 mEq. liter demonstrated that greatly increased extracellular Na concentration does not acutely depress renal function. Hypernatremia of this magnitude did not depress any of the physiologic parameters measured. In spite of the high urine flows in this series, sodium urine-plasma (U P) ratios in excess of 1.5 were obtained. The ability of the kidney to concentrate Na above plasma levels during severe alkalosis is thus demonstrated. Although Na clearance of 11 ml. minute was achieved in series 3 (table I), the actual output of Na, even in the last period, did not quite equal input by infusion. This inequality formed the major basis for increase in plasma Na concentration. Some loss of weight due to dehydration caused by the solute diuresis was found in the experimental group in series 3. The average loss of 0.8% body weight at the conclusion of the experiment played no role in the progressive increase in plasma Na concentration found.

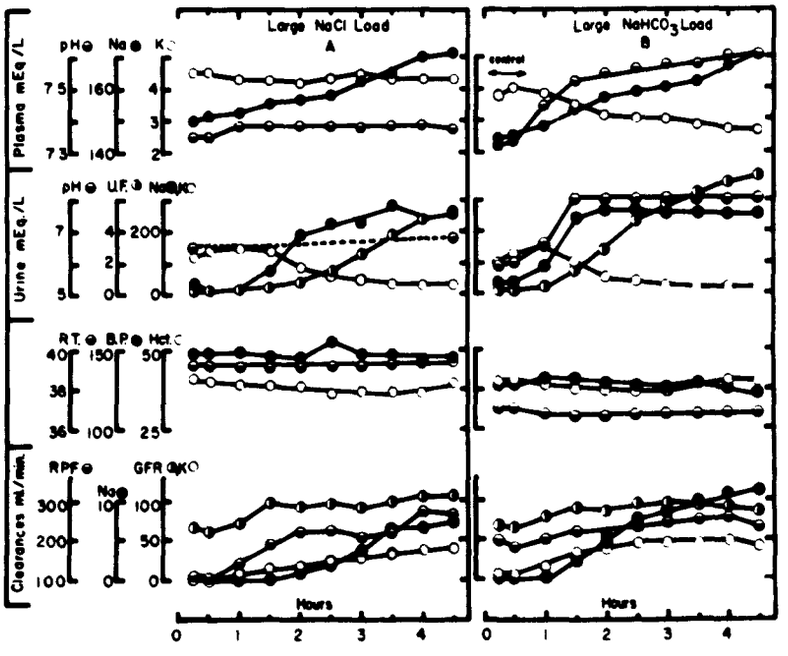

FIGURE 3

See legend for figure 1. Values are shown for 1 dog (3A) given 0.9% NaCl at 4.0 ml. minute for the 45-minute pre-control and 30-minute control period and 3.6% NaCl at 4.0 ml. minute for the 240-minute test period. Average of 3 dogs (3B) handled as described above during pre-control and control periods, but given 5.2% $NaHCO_3$ at an average infusion rate of 3.7 ml. minute during the 240-minute test period. Dog weight in 3A was 23 kg.; average dog weight in 3B was 17.9 kg.

Bicarbonate loading, in addition to causing an increase in plasma and urine pH, also caused a marked increase in both plasma and urine bicarbonate concentration (table II). The bicarbonate U P ratio rose, from a low approximately 0.005 during control, to the range of 9 decreasing to 4 during the infusion. During the last 3 hours, bicarbonate excretion averaged greater than 1.6 mEq. minute, while bicarbonate clearance approximated 40 ml./minute. A maximal reabsorption of 2.7 mEq./minute was found. While the pattern of reabsorption showed an increase correlated with the increase in plasma concentration, an even better correlation was obtained with the alteration in glomerular filtration rate. In terms of bicarbonate reabsorbed per 100 ml. of glomerular filtrate, reabsorption increased from 2.12 mEq. minute during control to 2.65 mEq. minute at the end of 4 hours of infusion. The highly alkaline pH therefore did not depress tubular reabsorptive capacity for bicarbonate.

4. DISCUSSION

No evidence of depression in the various parameters of renal function measured were apparent with acute alteration of arterial pH by $NaHCO_3$ loading. In a previous study similar results were obtained when arterial pH was elevated by hyperventilation (1). Other than the alteration in electrolyte balance, no untoward acute effects could be demonstrated.

The reports in the literature in regard to the toxicity of chronic administration of $NaHCO_3$ (2-8) deserve to be re-examined critically. Such evaluations in many instances lead to the conclusion that the reported renal depression with $NaHCO_3$ administration was not shown to be a cause-and-effect relationship. Many cases involved dehydration and electrolyte disturbances due to prolonged vomiting or diarrhea, or both—not caused by the alkali administration. In some unusual cases, dehydration may have been caused by $NaHCO_3$ ad-

TABLE II

Effect of bicarbonate loading on plasma and urine acid-base balance

	Control		Bicarbonate loading			
	Time (min.)					
	15	30	90	150	210	270
	Plasma					
pH	7.34	7.34	7.53	7.63	7.65	7.69
Total CO_2 (mEq. liter)	22.3	22.7	25.6	37.2	43.8	44.6
HCO_3 (mEq. liter)	21.1	21.5	24.7	36.2	42.6	43.5
GFR (ml. min.)	51.1	59.4	90.0	110.2	103.4	91.8
HCO_3 clearance (ml. min.)	0	0	21.9	44.2	39.4	35.7
	Urine					
pH	6.26	6.26	8.10	8.02	8.00	8.02
Total CO_2 (mEq. liter)	<0.1	<0.1	228.1	198.4	198.4	178.5
HCO_3 (mEq./liter)	<0.1	<0.1	225.9	196.0	196.1	176.4
Urine flow (ml./min.)	0.18	0.21	2.39	8.17	8.57	8.83
HCO_3 excreted (mEq. min.)	0	0	0.54	1.60	1.68	1.55
HCO_3 reabsorbed (mEq. min.)	1.08	1.28	1.68	2.39	2.73	2.44
HCO_3 reabsorbed (mEq. min./100 ml. GFR)	2.12	2.17	1.87	2.17	2.65	2.65

Results of one experiment from series 3B (table I). After control period, dog was given 5.2% $NaHCO_3$ at 4.0 ml. min. until end of experiment. Dog weighed 18.05 kg.

ministration but only due to the magnitude of administration. In these cases, NaCl of equal osmotic value might well have had the same end result.

The possible effects of massive $NaHCO_3$ administration must be considered. Most important are the effects of depression of plasma K concentration and the tendency to produce tetany at elevated pH. Obviously, when extreme, these alterations may in themselves lead to serious consequences. On the basis of this study as well as others (9-14, 21) it would seem to be difficult to reach critical levels with acute administration alone.

The finding of a decrease in renal resistance concomitant with the elevation of plasma pH due to $NaHCO_3$ loading is in agreement with the results of Franglen et al. (14). Dowds et al. (22), however, found little change in renal vascular resistance with changes in pH caused by hypercapnia and hyperventilation, while Emanuel et al. (23) reported a significant increase in renal resistance when the plasma pH was elevated by hyperventilation. The basis of the conflicting results may reside in differences in infusion composition and rate of administration, in surgical procedures employed, as well as in the methodology of producing the alteration in pH.

The effect of decrease in plasma K concentration and intracellular K content on glomerular filtration rate is similarly disputed. Blake (24) has reported that loss of intracellular K has a depressing effect on creatinine clearance but no causal relationship was established. In opposition to Blake, Roberts et al. (21) have shown that reduction of plasma K concentration from 4.00 to 2.50, with $NaHCO_3$ infusion, does not depress the glomerular filtration rate. Also in opposition to Blake are the results of this investigation, as well as Franglen's (14), in which the alterations in creatinine clearance and intracellular K content were strikingly divergent. The increase in creatinine clearance found in the latter two studies was due presumably to some effect of the solute loading (25). It is important to note that such an increase in GFR occurred despite the major decrease in plasma K concentration and intracellular K content (table I). The difference in results of Blake from those of Roberts, Franglen, and ourselves is not apparent.

The classical studies of Pitts et al. (26, 27) on the reabsorption of bicarbonate, in both the dog and man, had earlier showed that glomerular filtration was not depressed by acute loading of bicarbonate. No measurement of renal blood flow or renal resistance was made. The one experiment reported upon in detail in man did show a progressive increase in the GFR. While the determination of K balance was not included in their studies, it may be assumed that the alteration was typical of those reported elsewhere under similar conditions.

The results of Roberts et al. (21), in a study designed to investigate the relationship between K and bicarbonate in blood and urine, showed that an infusion of 0.6 mEq. minute of bicarbonate, for approximately 2 hours, did not depress renal function as judged by GFR and excretion patterns. Franglen et al. (14), in a thorough study of the effect of alkalosis on renal function and K excretion, also demonstrated the lack of renal depression with bicarbonate loads of 18 gm. given intravenously over a 2-hour period. The results of Van Goidsenhoven also support the viewpoint that administration of $NaHCO_3$ does not cause renal depression. In their study, 33 patients with gastric or duodenal ulcerations were given massive amounts of $NaHCO_3$ by constant gastric tube drip, throughout 24 hours for periods up to three weeks, without causing renal damage. Lastly, in the present study, it was demonstrated in dogs that over 50 gm. of $NaHCO_3$ could be administered intravenously in 4 hours, at a rate of 2.5 mEq. minute, without any apparent acute detrimental renal effects. On a weight basis, in a 70 kg. man, this would be equivalent to a load of 195 gm. of $NaHCO_3$ given at the rate of nearly 10 mEq. minute.

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